

# **Straight and Divergent Pathways to Cognitive State: Seven Decades of Follow-Up in the British 1946 Birth Cohort**

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## **Abstract**

**Background:** Using the British 1946 birth cohort we previously estimated life course paths to the Addenbrooke's Cognitive Examination (ACE-III).

**Objective:** We now compared those whose ACE-III scores were expected, worse and better than predicted from the path model on a range of independent variables including clinical ratings of cognitive impairment and neuroimaging measures.

**Methods:** Predicted ACE-III scores were categorized into three groups: those with Expected (between -1.5 and 1.5 standard deviation; SD); Worse (<-1.5 SD); and Better (>1.5 SD) scores. Differences in the independent variables were then tested between these three groups.

**Results:** Compared with the Expected group, those in the Worse group showed independent evidence of progressive cognitive impairment: faster memory decline, more self-reported memory difficulties, more functional difficulties, greater likelihood of being independently rated by experienced specialist clinicians as having a progressive cognitive impairment, and a cortical thinning pattern suggestive of preclinical Alzheimer's disease. Those in the Better group showed slower verbal memory decline and absence of independently rated progressive cognitive impairment compared to the Expected group, but no differences in any of the other independent variables including the neuroimaging variables.

**Conclusion:** The residual approach shows that life course features can map directly to clinical diagnoses. One future challenge is to translate this into a readily usable algorithm to identify high-risk individuals in preclinical state, when preventive strategies and therapeutic interventions may be most effective.

**Keywords:** Addenbrooke's Cognitive Examination-III, birth cohort, cognitive state, life course, residuals

## **INTRODUCTION**

Dementia is one of the most feared conditions in later life, with significant impact on daily function, quality of life and survival, and on needs for informal and paid support [1]. With the increasing availability of long-term cohort studies, a better understanding is being gained of how influences on dementia risk unfold across the life course [2]. Using the British 1946 birth cohort, we previously estimated direct and indirect paths across the life course to cognitive state at age 69, measured by the Addenbrooke's Cognitive Examination (ACE-III) [3]. The strongest influence on the ACE-III was from childhood cognition, largely operating through cognitive ability in midlife, measured by the National Adult Reading Test (NART). Educational attainment and midlife occupational complexity were modestly and independently associated with the ACE-III. There was a small independent negative association between the apolipoprotein gene  $\epsilon 4$  allele (*APOE*  $\epsilon 4$ ) and the ACE-III score, not mediated by childhood cognition or the NART [3].

As with all regression analysis, path modelling emphasizes trends. However, this provides little insight into individuals with ACE-III scores that significantly deviate from these trends. We therefore aimed to characterize those who scored better or worse than predicted from our model in comparison to those who performed at approximately the predicted level. To do this, we compared these groups on a range of independent life course variables that potentially indicate clinically significant cognitive decline. Second, to gain mechanistic insights, we compared these groups on a range of neuroimaging outcomes available in a smaller sub-study. Since, as noted, our original path model demonstrated that cognitive function is relatively stable across the life course [3], we hypothesized that those in the worse group would show evidence of progressive cognitive decline. We also expected that those in the better group would show evidence of preserved cognitive function to a greater extent than those with ACE-III scores in the predicted range.

## **METHODS**

### *Participants*

The MRC National Survey of Health and Development (NSHD; the British 1946 birth cohort) originally consisted of 5,362 male and female singleton births within marriage in England, Wales and Scotland in on week of March 1946 (<http://www.nshd.mrc.ac.uk/nshd>). At age 69, the 2,698 individuals still alive and with a known current address in mainland Britain were invited to have a home visit by a trained nurse; 2,149 (79.7%) completed a visit and a further 55 (2.0%) completed a postal questionnaire instead. Of the original cohort, 1,026 (19.1%) had died, 578 (10.8%) were living abroad, 22 (0.4%) asked for their participation to be restricted to postal contacts, 621 (11.6%) had previously withdrawn from the study, and 417 (7.8%) had been lost to follow-up [4]. Those not interviewed at age 69 showed similar *APOE*  $\epsilon 4$  frequency to those included, but had lower childhood cognition and NART scores, and were more likely to be disadvantaged in terms of father's social class, mother's education, own education, and occupational complexity. Those not interviewed also had poorer physical health, partly explained by socioeconomic and cognitive characteristics [4]. Of those interviewed at age 69, there were no differences in any of the path variables between those with and without ACE-III data, except for a slight trend for the ACE-III to be missing in those with no educational qualifications (chi square=9.5,  $p=0.05$ ). Frequencies for each category of *APOE* group, childhood and midlife socioeconomic position, and educational attainment, and means and SDs for the ACE-III and NART, have been previously detailed [3].

#### *Standard protocol approvals, registrations, and patient consents*

Current ethical approval for the MRC National Survey of Health and Development was granted by NRES Queen Square Research Ethics Committee (14/LO/1073) and Scotland A Research Ethics Committee (14/ SS/1009). All study members provided written informed consent. No information is provided in this manuscript that can identify any individual study member.

#### *Measures*

We measured the total score of the ACE-III. This is a cognitive test widely validated as a screening tool for cognitive deficits in all dementias [5]. The ACE-III has five domains: attention and orientation (scored 0–18), verbal fluency (0–14), memory (0–26), language (0–26), and visuospatial function (0–16). The maximum total score is 100 with high scores meaning better cognitive function. Due to the inclusion of verbal fluency, the distribution of the total score is quasi-normal and avoids the pronounced ceiling effect of most cognitive state tests. A customized version of the ACE-III was administered by iPad using ACEMobile (<http://www.acemobile.org/>); where this was not possible, a paper version was used. All offline scoring was undertaken by trained personnel. Of the 2,149 participants who had a home visit, 32 refused or were unable to undertake the ACE-III. Of the remaining 2,117, 35 undertook but did not complete this; and for the remaining 2,082, data for 320 were lost through equipment failure. Thus, complete ACE-III data were available for 1,762 participants, 82.0% of those who received a home visit.

The path predictor variables from our previous study were:

1. At least one copy of the *APOE*  $\epsilon$ 4 allele.
2. Father's occupational social class (professional, managerial, intermediate, skilled manual, semiskilled manual, or unskilled according to the UK Registrar General).
3. Mother's education (primary only versus secondary or any formal qualifications)
4. Childhood cognition at age eight years (sum of 4 tests: reading comprehension, word pronunciation, vocabulary, and non-verbal reasoning).
5. Educational attainment (highest qualification by age 43).
6. Midlife occupational complexity coded by the National Statistics Socio-Economic Classification (NS-SEC) of the job held at age 53 or earlier if this was missing [6]: higher managerial; administrative and professional; lower managerial, administrative and professional; intermediate; small employers and own account workers; lower supervisory and technical occupations; semi-routine; routine.
7. National Adult Reading Test (NART) at age 53 years, a test of word pronunciation using 50 irregular words of increasing difficulty [7].

Based on these variables, the original path model is shown in Fig. 1.

A range of independent variables were used to inform a clinical impression of cognitive impairment: objective memory impairment at age 53 ( $\geq 1.5$  SD below the mean total score of a word-learning task [8]); degree of decline in this total score between ages 53 and 69; self-reported memory problems since age 60; a doctor diagnosis of memory problems since age 60 (and if so, age at diagnosis); any functional impairment, assessed by self-reported activities of daily living at age 69 (difficulty with any of: taking the right amount of medication, doing routine housework or laundry, preparing a hot meal, doing paperwork and paying household bills, shopping for food, and getting out of the home), and by self-reported everyday social function (mental fatigue while participating in a social activity for 1 h) at age 68. To help distinguish whether any impairment was recent onset or lifetime, mild learning disability was classified at age 15 [9]. To help clarify the nature of any impairment, cerebrovascular risk was indicated by self-reported stroke at age 69; and depression of potential diagnostic severity was based on a validated severity threshold on the 28-item version of the General Health Questionnaire (a symptom score of  $\geq 5$  when items were recoded to 0-0-1-1) [10]. Three senior clinicians in relevant medical disciplines (GL: old age psychiatry; JS: neurology; DD: geriatric medicine) then reviewed this information and independently classified the clinical status of study members who scored below the clinically validated ACE-III threshold of 82 (n=115) plus those who scored above this threshold but were recorded elsewhere by a doctor as having memory problems. Instructions were open-ended for how to formulate the ratings; however, for the present study all were dichotomized to progressive cognitive impairment versus any other (e.g., psychiatric, premorbid, uncertain). If there was any disagreement, a majority rating was accepted.

Finally, a range of neuroimaging outcomes were provided by Insight 46, a sub-study of NSHD (original N=502). A Biograph mMR 3 T PET/MRI scanner (Siemens Healthcare, Erlangen) allowed simultaneous acquisition of dynamic amyloid PET and MRI data, from which the following variables were derived: total brain, hippocampal and white matter hyperintensity volume (adjusted for total intracranial volume) [11], amyloid- $\beta$  burden

(estimated by  $^{18}\text{F}$  florbetapir standardized uptake value ratio [12]), lobe-specific cortical thickness, and a cortical thinning signature for Alzheimer's disease (AD) using the Mayo AD signature, comprising entorhinal, fusiform, inferior and middle temporal cortical regions ('ADsig Mayo') [13,14]. Insight 46 participants were also administered the Preclinical Alzheimer Cognitive Composite (PACC), a set of four cognitive tests selected to track subtle cognitive decline in the preclinical phase of AD [15]. The original PACC is composed of 4 tests: the Mini-Mental State Examination, Logical Memory IIa from the Wechsler Memory Scale-Revised, Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised, and the Free and Cued Selective Reminding Test (FCSRT). For Insight 46, the FCSRT was replaced with the 12-item Face-Name test (FNAME-12) to avoid potential overlap with the word-learning task noted at the beginning of the previous paragraph [16].

### *Statistical methods*

Path modelling was originally used to quantify associations between each predictor variable and the ACE-III [3]. The model was adjusted for sex, and it incorporated full information maximum likelihood (FIML) parameter estimates to include those with item-missingness [17]. All statistical analyses were conducted using STATA V.15 [18].

As previously reported [3], goodness-of-fit statistics indicated that the model was an excellent representation of the data: chi-square=0.15,  $p=1.0$  for analytic versus saturated model; Root mean square error of approximation (RMSEA; a measure of the discrepancy in fit per degrees of freedom)=0,  $p=1.0$ ; comparative fit index (CFI)=1.0. Residuals of ACE-III performance were computed from a separate linear regression of predicted and actual ACE-III scores. These residuals were standardized to the available sample and categorized into three groups: Expected (between -1.5 and 1.5 SD); Worse (<-1.5 SD); Better (>1.5 SD). Between-group analyses using the Expected group as the reference then compared the independent variables, including clinical ratings and neuroimaging measures. Linear and logistic regression tests were used for continuous and categorical variables, respectively, and were adjusted for sex. For analyses

investigating the neuroimaging metrics, residuals were standardized to the neuroimaging sub-sample and analyses were adjusted for age at scan and sex. Total intracranial volume was additionally adjusted for models including brain volume, hippocampal volume and white matter hyperintensity. White matter hyperintensity volume was log transformed.

## **RESULTS**

The maximum N for the ACE-III was 1762 but due to missing data one participant failed to receive a predicted score from the path model, resulting in a final sample size of 1,761.

1,572 (89.2%) had residual scores within the predicted range; 127 (7.2%) had scores that were worse than predicted; and 62 (3.5%) had scores that were better than predicted. For descriptive purposes, Fig. 2 shows these predicted ACE-III scores plotted against raw scores, by residual group, Fig. 3 shows frequency of actual ACE-III scores by residual groups, and Table 1 shows Predicted (from path analysis) and actual ACE-III total scores, grouped by those in the Expected, Worse ( $<-1.5SD$ ) and Better ( $>1.5SD$ ) residual groups.

[Figures 1, 2 and 3 about here]

[Table 1 about here]

Table 2 shows means, SDs, and proportions for the independent variables by the three residual groups. Those in the Worse group were more likely to have been classified with mild adolescent learning disability, to have had poor memory performance at age 53 and faster memory decline from age 53 to 69, were more likely to report difficulties with memory and instrumental activities of daily living at age 69. Clinician ratings were more likely to identify the Worse group as having a progressive cognitive impairment than those in the Expected group. They also showed higher frequency of stroke. On the other hand, there was no group difference in mental fatigue during social activities or case-level emotional symptoms at age 69. There were fewer differences between the



Better and Expected groups, except that those in the Better group showed less memory decline from age 53 to 69, and none were rated as having a progressive cognitive decline. There was a trend towards this group being less likely to have case-level emotional symptoms at age 69 ( $p = 0.1$ ).

[Table 2 about here]

Residuals were re-standardized to the neuroimaging sample, and Table 3 shows differences in neuroimaging outcomes in those in the Worse and Better residual groups compared with those in the Expected group. For descriptive purpose only, means for the volumetric measures in this table are unadjusted. Consistent with a previous report [19], those in the neuroimaging sample were more advantaged in terms of parental characteristics and own educational and occupational attainment. There were no differences between the groups in total, hippocampal or white matter hyperintensity volumes. However, compared to the Expected group, the Worse group showed significantly lower frontal and temporal cortical thickness, and lower thickness for the AD signature regions (entorhinal, fusiform, inferior, and middle temporal).

[Table 3 about here]

## **DISCUSSION**

The title of this article echoes that of a 1990 book edited by Robins and Rutter: 'Straight and devious pathways from childhood to adulthood' [20]. Using the 1946 British birth cohort we extended a previous path model linking a range of key variables across the life course to cognitive state (ACE-III) [3]. Further to that, here we investigated predictors of ACE-III performance which significantly diverged from prediction by the model regression, represented as more than 1.5 SD divergence in either direction. Thus, divergence was relative to the path variables so that, by definition, factors external to the path model were responsible for this divergence. Strikingly, those in the Worse group showed independent evidence suggestive of progressive cognitive impairment, including, on the whole, faster memory decline from midlife to early old age, more likelihood of self-reported memory difficulties at the latter

age, greater difficulty with instrumental activities of daily living, greater likelihood of being independently rated by experienced specialist clinicians as having a progressive cognitive impairment, and a cortical thinning pattern suggestive of preclinical AD. Regarding the latter, it is worth noting that cortical thickness was independent of amyloid- $\beta$  status in Insight 46 [14], which in turn was similarly distributed between the Expected and Worse residual groups in the present study. Although the absolute numbers were small, the Worse group were also significantly more likely to have been classified by the study as having mild learning disability in adolescence. This is consistent with evidence from the 1921 Scottish Birth Cohort, that childhood cognition predicts late-onset dementia [21]. Correspondingly, there was a trend towards relative advantage with most of the independent variables in the Better group, although this only reached conventional levels of statistical significance for slower verbal memory decline and absence of independently rated progressive cognitive impairment; this advantageous trend was not evident in the neuroimaging variables.

Strengths of this study are the large population-based sample, with a wide range of prospective data across nearly 70 years of the life course. These data include cognitive test scores in childhood, which are not always available from school records, and cannot be estimated from educational attainment. However, these strengths need to be considered alongside some limitations. Most important, the distribution of the ACE-III placed constraints on residual group assignment. In particular, since the Better group scored  $>1.5SD$  above prediction by definition, i.e., by  $\sim 7$  points, only participants with a predicted score less than  $\sim 93$  could potentially be classified to this group. Thus, the negative skew of the ACE-III (illustrated in Fig. 3) limited this potential. This could also have limited the comparison of the Better and Expected groups on the independent variables. It should also be noted that the 1946 birth cohort is confined to Britain, was born during unusual conditions immediately following World War II, and is entirely of White European heritage. Generalization to different ages, cultures, and social and environmental conditions is therefore uncertain.

We have emphasized prediction of those in the Worse residuals group, but what about those in the Better group? As noted, individuals in this group scored better on the ACE-III than would be predicted from their disadvantaged status with respect to genetic risk, parental social position, cognitive development, and educational and occupational attainment. Further work is required to identify potential independent protective factors against cognitive impairment in this group. For example, although not reaching conventional levels of statistical significance, there was an indication of lower stroke risk and better mental health in this group compared to the Expected group, although the directionality of this association is unclear. A more detailed investigation of health trajectories over the life course, along with other independent factors that potentially mitigate the influence of genetic, social, early cognitive and attainment disadvantage on late midlife cognitive state is therefore warranted. It is worth noting that the positive residual perspective in the present study is consistent with the concept of cognitive reserve. As developed by Stern [22], the latter in essence maintains that there are factors that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to cause functional impairment. More specifically in the present context, cognitive reserve has been invoked to understand discrepancies between measured and expected cognitive performance quantified as residual variance in performance after accounting for demographic factors and neuropathology [23]. We suggest that modelling residual scores for cognitive state within a life course epidemiological framework is a potentially effective way of identifying individuals at risk of a clinical diagnosis, including those who screen within normal cognitive limits. For example, in the present study a substantial proportion of those in the Worse residual group nevertheless scored above the ACE-III impairment threshold (Fig 2); reliance on such a cross-sectional threshold can therefore miss individuals who are declining from a relatively high level. With important implications for following up the present study, Stern and colleagues also showed that change in residual memory variance among initially non-demented older adults was a better predictor of incident dementia than residual memory variance measured at one time-point [24].

In summary, we found that those in the British 1946 birth cohort who scored worse on the ACE-III at age 69 than predicted from *APOE* ε4 status, parental social position, cognitive development, and educational and occupational status, showed independent evidence consistent with increased risk of clinically significant cognitive decline. This suggests that the residual approach has strong utility in population-based research, and in this study that life course features can map directly to clinical diagnoses. One future challenge is to translate this population-based research strategy into a readily usable algorithm for clinical practice and public health settings, to identify high-risk individuals in preclinical state, when preventive strategies and therapeutic interventions may be more effective than further along the clinical course.

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Table 1. Predicted (from path analysis) and actual ACE-III total scores, grouped by those in the Expected, Worse (<-1.5SD) and Better (>1.5SD) residual groups

	Overall (N=1761)	Expected (N=1572)	Worse (N=127)	Better (N=62)
Predicted ACE-III (mean, SD, range)	91.54, SD=4, range=80-100	91.82, SD=4, range=80-99	89.73 SD=4, range=81-98	88.04 SD=2, range=82-93
Actual ACE-III (mean, SD, range)	91.55, SD=4, range=59-100	92.36, SD=5, range=77-100	78.88 SD=6, range=59-90	96.55, SD=2, range=90-100

Table 2. Means (standard deviation) and proportions for the independent variables by the Predicted, Worse and Better residual ACE-III groups

<b>Independent variable</b>	<b>Expected group</b>	<b>Worse group</b>	<b>Better group</b>
Adolescent mild learning disability	1.0%	4.7%*	0.0%
Memory impairment age 53	4.0%	15.0%**	7.0%
Memory change age 53 to 69 <sup>a</sup>	-2.4 (4.9)	-4.1 (5.4)**	-0.9 (5.3)
Self-reported memory difficulties age 69	7.0%	14.0%**	5.0%
Any difficulty with IADL age 69	9.0%	19.0%**	8.0%
Mental fatigue during social function age 68 (mean, SD)	0.81 (1.13)	0.85 (1.32)	0.93 (1.32)
Stroke age 36 to 69	4.0%	7.0%*	2.0%
'Case'-level emotional symptoms age 69	14.0%	16.0%	8.0%
Clinical rating of progressive cognitive impairment	0.7%	23.6%**	0.0%
Clinical rating of 'other' cognitive impairment	1.6%	37.0%*	0.0%*

IADL, instrumental activities of daily living; SD, standard deviation

<sup>a</sup> maximum score for this test is 45

\*p<0.05; \*\*p<0.01

Table 3. Means (standard deviation) and proportions for neuroimaging and cognitive outcomes in those with Worse and Better compared to Predicted residual ACE-III scores

<b>Independent variable</b>	<b>Expected group</b>	<b>Worse group</b>	<b>Better group</b>
Brain volume (% of TIV)	77.0%	76.0%	78.0%
Brain volume, mL (mean, SD)	1102.52 (95.06)	1079.49 (104.13)	1083.14 (87.38)
Hippocampal volume (% of TIV)	0.22%	0.21%	0.22%
Hippocampal volume, mL (mean, SD)	3.14 (0.32)	3.01 (0.44)	3.04 (0.30)
White matter hyperintensity volume (% of TIV)	0.40%	0.40%	0.23%
White matter hyperintensity volume, mL (median, IQR)	3.12 (1.55, 6.75)	3.46 (1.97, 6.92)	2.59 (1.90, 3.30)
Total intracranial volume, mL (mean, SD)	1435.22 (128.42)	1418.34 (116.36)	1383.06 (113.11)
Amyloid- $\beta$ status (% A $\beta$ positive)	20.0%	21.0%	25.0%
Cortical thickness (mm)			
Frontal	2.70 (0.1)	2.69 (0.1)**	2.78 (0.1)
Occipital	2.19 (0.1)	2.16 (0.1)	2.18 (0.1)
Temporal	2.86 (0.1)	2.81 (0.1)**	2.86 (0.1)
AS signature	2.89 (0.1)	2.84 (0.1)**	2.88 (0.1)
PACC total score	0.03 (0.7)	-0.48 (1.2)**	-0.09 (0.6)

TIV, total intracranial volume; SD, standard deviation; IQR, interquartile range; PACC, Preclinical Alzheimer Cognitive Composite, standardized

\*p<0.05; \*\*p<0.01

Fig. 1. The original model describing life course paths to the Addenbrooke's Cognitive Examination third edition (ACE-III).

Figure from Richards M, James SN, Sizer A, Sharma N, Rawle M, Davis DHJ, Kuh D (2019) Identifying the lifetime cognitive and socioeconomic antecedents of cognitive state: seven decades of follow-up in a British birth cohort study. *BMJ Open* **9**, e024404, under the terms of the Creative Commons CC BY 4.0 license.

Fig. 2. Actual ACE-III scores plotted against predicted scores by residual group

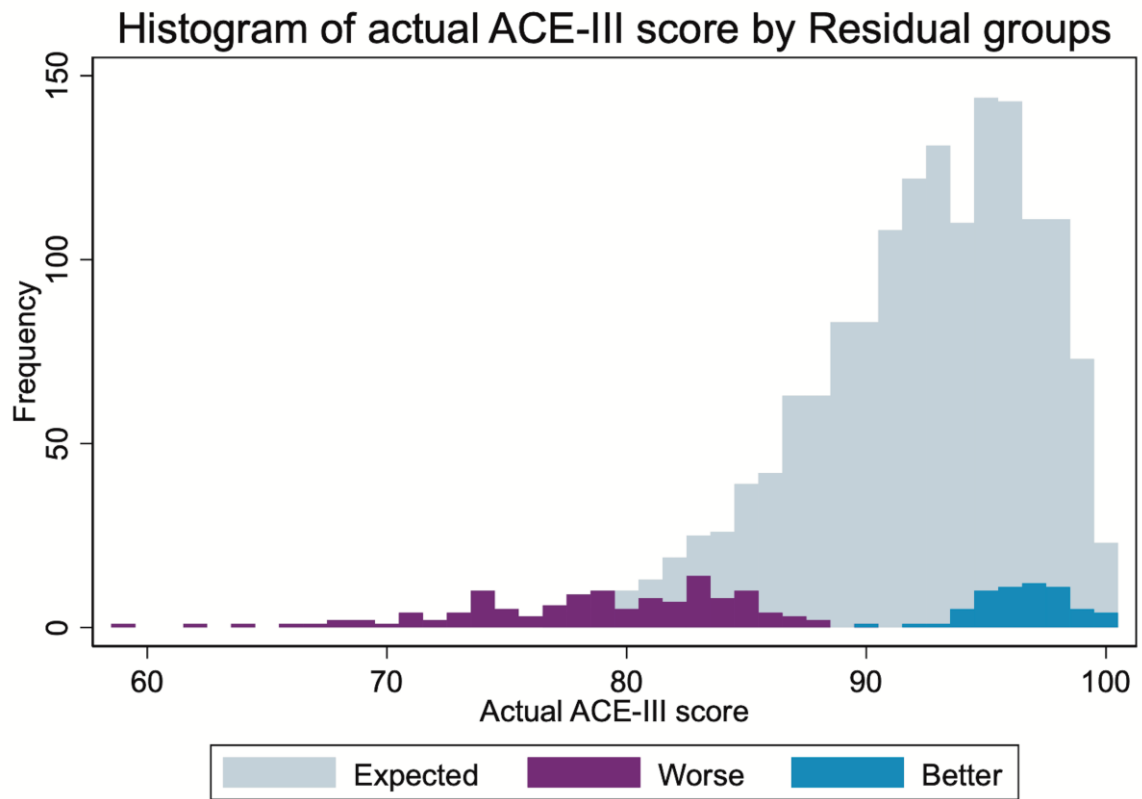


Fig. 3. Frequency of actual ACE-III scores plotted against residual groups

